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The two graduate students supported by this augmentation award have graduated and started Post-Doctoral studies in two outstanding laboratories. I will first summarize the data collected by these students and then consider some of the fascinating theoretical observations that arise from this data. Finally the publications arising from the studies by these students will be listed at the end of this document.

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Sharleen Argamaso-Hernan (Completed Ph.D. Fall 1995)

The two graduate students supported by this augmentation award have graduated and started Post-Doctoral studies in two outstanding laboratories. I will first summarize the data collected by these students and then consider some of the fascinating theoretical observations that arise from this data. Finally the publications arising from the studies by these students will be listed at the end of this document.

Photoentrainment in mammals - Summary of Results. In mammals the circadian clock is located within the SCN and is regulated by photoreceptors within the eye. Loss of the eyes blocks all circadian responses to light in every mammal examined (cf. all other vertebrates) (Foster, Provencio, Hudson, Fiske, De Grip, & Menaker, 1991; Nelson & Zucker, 1981). While we know that the entraining photoreceptors are ocular, the few studies undertaken all show that there are significant differences between the processing of light information for image-forming visual responses and photoentrainment. The route by which light information reaches the circadian system (the retinohypothalamic tract RHT) is anatomically, developmentally and physiologically distinct from the visual projections (Moore & Klein, 1974; Pickard, Turek, Lamperti, & Silverman, 1982) Moore, 1995 #1474. In addition, circadian responses to light seem to differ from visual responses; the threshold for phase shifting circadian rhythms is relatively high, and intensity-duration reciprocity holds for stimuli of very long durations (up to 45 minutes) (Takahashi, DeCoursey, Bauman, & Menaker, 1984).

The photoentrainment pathway constitutes a minute portion of the eye, obscured by the large number of photoreceptors and inner retinal neurons devoted to image formation. As a result, the role of rods, cones and other retinal neurons in entrainment has been difficult to study. In recent years we have used retinally degenerate models as "reduced preparations". Studies have correlated the loss of retinal elements with any effects on photoentrainment. Our first experiments in this area used mice homozygous for *retinal degeneration* (*rd/rd*). These mice experience a massive degeneration of the rods and cones. By 60 days of age all rod cells have degenerated, and between 90 and 150 days of age even the crudest electrophysiological and behavioral responses to bright light have disappeared (Provencio, Wong, Lederman, Argamaso, & Foster, 1994). In the mouse retina, approximately 97-98% of all photoreceptors are rods, and although all rods degenerate in the *rd/rd* retina a few cone cells remain in animals over one year of age. These cones lack outer segments and constitute only 2-5% of the cone cells found within the normal (+/+) retina. As a result, the *rd/rd* eye at about one year of age contains approximately 0.09% of its original number of photoreceptor cell bodies (perhaps 4,500 cells), and with increasing age, cone cell loss continues. To determine the impact of photoreceptor loss on the circadian system, the effects of a standardized light pulse on phase shifting the freerunning locomotor rhythm were determined in three genotypes of mice (*rd/rd, rd/+, +/+*) from the same C57BL strain. Despite the loss of visual photoreceptors in *rd/rd* mice, these animals show circadian responses to light that were indistinguishable from mice with phenotypically normal retinas (*rd/+, +/+*). The irradiance required to produce both saturating and half-saturating responses was the same for all groups. It is important to stress that not only does some photosensitivity remain in mice with degenerate retinas, but the circadian photosensitivity shown by these animals is not different from the sensitivity of animals with normal retinas. Significantly unattenuated sensitivity is maintained in animals greater than two years of age, demonstrating that the sensitivity of the circadian system to light does not parallel photoreceptor loss in the *rd/rd* mouse (Provencio, et al., 1994).

Another retinal mutation, *retinal degeneration slow* (*rds/rds*) has provided a second approach to the question of which elements in the eye mediate circadian responses to light. In *rds/rds* mice, the retina undergoes normal development until the first postnatal week, then both rod and cone photoreceptors fail to develop outer segments and then gradually degenerate. In *rds/rds* mice approximately half of all the rods and cones have degenerated by 3 months, and most photoreceptors seem to have degenerated by 1 year of age, for review see (Argamaso, Froehlich, McCall, Nevo, Provencio, & Foster, 1995). Our recent studies have shown that circadian responses to light are identical in *rds/rds*, *rd/rd* and +/+ genotypes (Argamaso, et al., 1995). This provides overwhelming evidence that the photoreceptive elements mediating circadian responses to light do not require an outer segment.

Until the studies on *rd/rd* mice it had been assumed that rods regulate circadian responses to light in mammals. This belief was based upon an action spectrum for phase shifting of locomotor activity rhythms in the golden hamster (*Mesocricetus auratus*) (Takahashi, et al., 1984). These data show a spectral maximum (λmax) around 500 nm, which correlates well with the absorbance (λmax = 502 nm) of the extractable rod photopigment in this species. More recent studies in rodents, however, have demonstrated the existence of cones with spectral sensitivities near 500 nm (Jacobs, Neitz, & Deegan, 1991), including hamsters, in which a single cone sensitivity has been identified between 505 - 506 nm (Calderone & Jacobs, 1995). Because the action spectrum for phase shifting locomotor rhythms cannot resolve differences between sensitivities at 502 nm (rod) or 506 nm (cone), the roles of rods and/or cones, therefore, remains uncertain in this species. Two types of cones have been identified in the normal mouse retina. Electroretinogram (ERG) and behavioral studies have shown two sensitivity maxima, a green-sensitive cone near 510 nm and an ultraviolet sensitive cone near 360 nm (Jacobs, et al., 1991). Our Action spectra for phase-shifting in aged (80 - 90 days) *rd/rd* (rodless) and +/+ mice show two spectral sensitivities around 510 nm and 360 nm, corresponding well with the absorption maxima of the two known mouse cone types (Provencio & Foster, 1995). By using RT-PCR techniques, followed by cloning and sequencing of the amplified cDNAs, low levels of both the green and UV cone opsin have been isolated from the aged *rd/rd* retina (animals > 2 years). However, rod opsin mRNA was not detected beyond approximately 1 year of age (Argamaso-Hernan & Foster, manuscript in preparation). On the basis of the molecular analysis, and the similarity of the action spectrum results with the spectral sensitivity of the known cones, the cones become strong candidates for circadian regulation. However it is worth stressing that although cone opsins and cell bodies remain in the *rd/rd* retina, most of the cones have been lost and the remaining cones lack outer segments. If the remaining cones do mediate circadian responses to light then one must propose a mechanism that can compensate for massive photoreceptor loss and loss of outer segments.

Theoretical Considerations: Perhaps the most surprising observation to emerge from our studies outlined above is that mammals which lack classical visual responses are still capable of regulating their circadian rhythms by light with unattenuated sensitivities. These data have led to the realization that two functionally distinct systems exist for processing light information in the mammal eye (and perhaps the other vertebrates). The "image-forming" photoreceptor system, which constructs a representation of the environment (classical vision) and the "non-image-forming" photoreceptor system, which instead detects changes in the overall quality of light at different times of day. In view of the different sensory demands of image detection and the regulation of biological clocks it is not surprising that two systems for processing light information have evolved. Support of this comes from recent studies which show that certain "blind" individuals can still regulate their circadian rhythms by light (Czeisler, Shanahan, Klerman, Martens, Brotman, Emens, et al., 1995).

The sensory ecology of photoentrainment. Our research effort to understand photoentrainment in mammals has concentrated on the search for the photoreceptors and their projections to the clock. As a result of this work however we began to consider in much greater detail the sensory ecology of the entrainment pathway and the features of the light environment at dawn and dusk that may be important for circadian regulation. During twilight, the quality of light changes in three important respects: 1) the amount of light, 2) the spectral composition of light, 3) and the source of light (i.e. the position of the sun). These photic parameters all change in a systematic way, and could be used by organisms to detect the phase of twilight. For example:

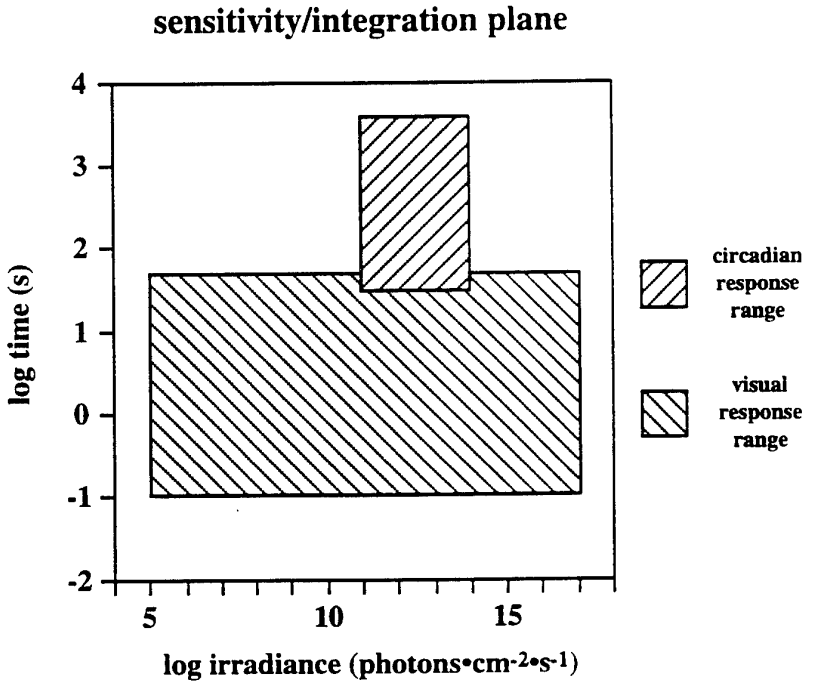
1) The amount of light. The unique anatomical and physiological features of the photic input to the SCN seem to protect the circadian axis from stimuli incapable of serving as reliable time cues. The circadian and visual systems occupy different regions of a theoretical plane where the *x* dimension is sensitivity and the *y* dimension is integration time (**Figure 1**). It is striking that in those animals studied the threshold for phase shifting circadian rhythms is significantly higher than that required to elicit visual responses. For example, hamsters can recognize optical gratings at a luminance level 200 times less than the level necessary to elicit phase shifts in locomotor rhythms (Emerson, 1980). This relative insensitivity of the circadian system may function to filter out "photic noise" (Nelson & Takahashi, 1991). The irradiance of starlight is approximately 9.3 x 10^8 photons.cm^{-2}.s^{-1} (total irradiance between 400 and 700 nm) while the irradiance of the full moon is approximately 32-fold greater (3 x 10^{10} photons.cm^{-2}.s^{-1} total irradiance between 400 and 700 nm) (Munz & McFarland, 1977). Both of these "photic noise" sources fall below the threshold for photoentrainment, and therefore cannot interfere with circadian function. Lightning could potentially "confuse" the circadian system. It can be 50 times greater than that of direct sunlight. In addition, shading by vegetation or cloud cover can greatly alter the amount of light falling upon an organism. As a result, any reliable measure of light level (and hence time of day) must compensate for local fluctuations. In view of these considerations, it is not surprising that the circadian system of those animals examined is very insensitive to light stimui of short durations. For example, the circadian system of the hamster is relatively insensitive to stimulus durations of less than 30 seconds (Nelson & Takahashi, 1991).

The circadian system needs to measure overall light levels in the environment (irradiance) and ignore brightness in particular areas of the sky (radiance). For image detection, the visual system maintains complete retino-topographic order. The eye focuses light onto a particular region of the retina, and this radiance information is then mapped to a specific position in the brain. By contrast, the circadian system requires measures of irradiance. Photoreceptors located beneath the skull or in the brain are unable to extract any image information, the overlying tissues scatter light to such an extent that all features are lost. By their very nature the pineal and deep brain photoreceptors of non-mammals are excellent irradiance detectors. But mammals lack extraretinal photoreceptors and are "forced" to use their eyes for photoentrainment, and the question has been how do mammals attempting to extract irradiance information compensate for a lens? The answer seems to be as follows. The retinal ganglion cells (RGCs) projecting to the SCN are relatively scarce and have extensive dendritic arbors. This reduces spatial resolution and increases sampling area. In addition, there is an absence of retinotopic order in RHT. RGCs project randomly to the retinorecipient areas of the SCN, which further blurs any image. These combined effects provide the SCN with irradiance information.

2) The spectral composition of light. In addition to large changes in irradiance, there are very precise spectral changes associated with twilight. Primarily there is an enrichment of the shorter wavelengths (< 500 nm) relative to the mid-long wavelengths (500 - 650 nm) at twilight. If the circadian system was capable of some form of spectral discrimination, and able to ratio changes in the relative amounts of short and long wavelength radiation, then it could determine the phase of twilight very accurately. Whether any animal circadian system uses spectral information remains unclear, but it is striking that mice seem to use at least two photopigments (λ_{max} at 511 nm and in the near-UV) to regulate their circadian responses to light. If wavelength discrimination is used by the mammalian circadian system for photoentrainment, and based on the assumption that photoentrainment evolved before image detection, then it is possible that multiple photopigments and wavelength discrimination may have evolved originally as a means of detecting changes in twilight. These mechanisms only later became specialized for contrast detection in the image-forming visual systems.

3) The position of the sun in the sky. The position of the sun in the sky is used by many different animals for time compensated sun-compass orientation, for review see (Wallraff, 1981). Whether this information is also used by organisms to entrain circadian systems remains a mystery. For this task radiance detection, and topographic mapping, would be required to determine the position of the sun. In this way perhaps the "classical" visual system does contribute to photoentrainment.

Figure 1.



Graphical representation of the response ranges of the visual and circadian systems. The response range of sensitivity (x-axis) and integration time (y-axis) of the circadian and visual systems are contained within their respective rectangles. Note that the circadian system is insensitive to light and requires stimuli of long durations relative to the visual system. The unique anatomical and physiological features of the photic input to the SCN protect the circadian system from stimuli that do not provide reliable time cues.

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Provencio

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